Drug Therapy of Nausea, Vomiting, Diarrhea and Constipation

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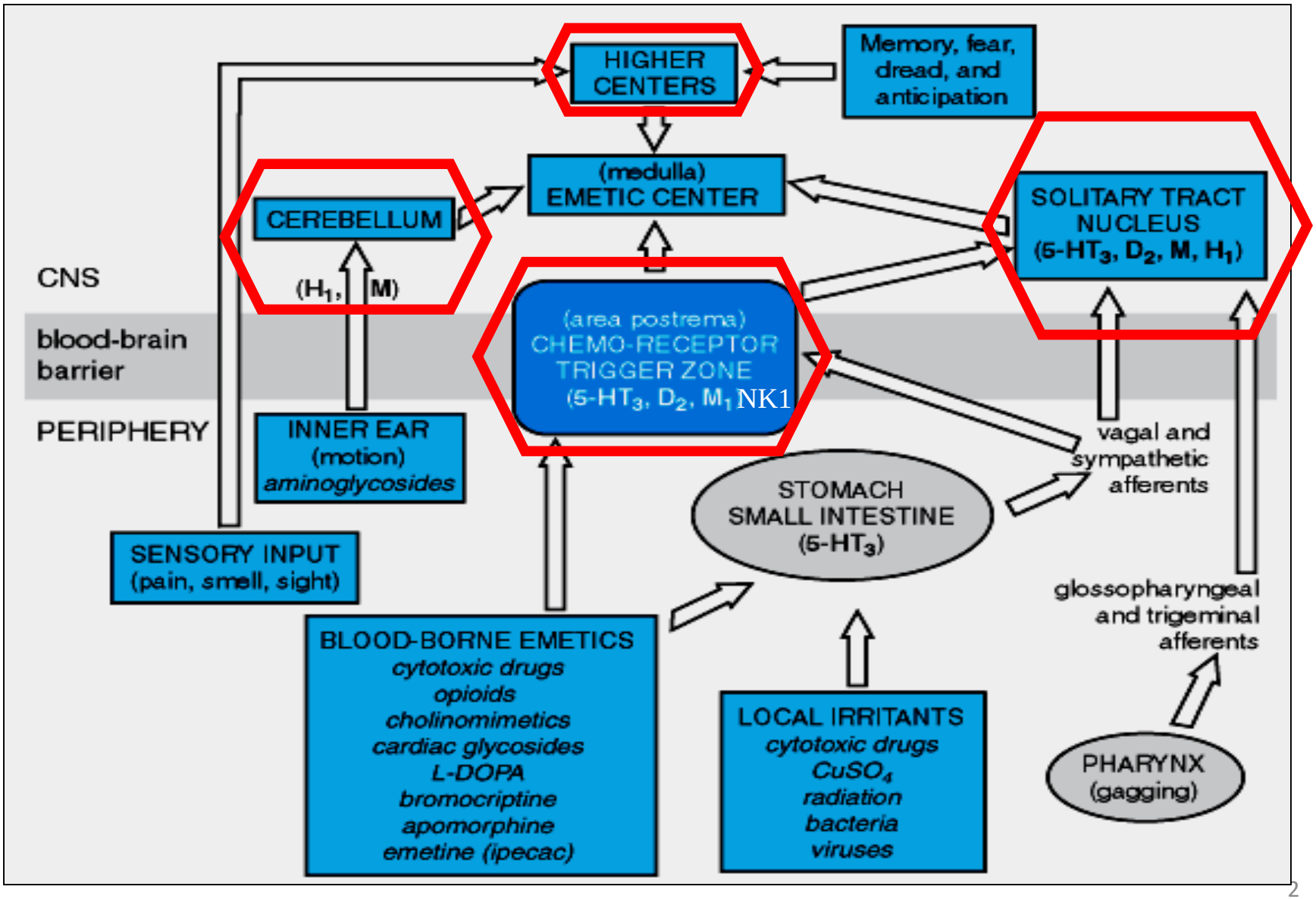
Mechanisms of Vomiting



Antiemetics and Antinauseants

1) 5-HT_3-Receptor Antagonists.
2) Neurokinin Receptor Antagonists.
3) Corticosteriods
4) D_2 Receptor Antagonists.
5) Antihistaminics and Anticholinergics.

	5-HT3-Receptor Antagonists *e.g., ondansetron, granisetron, dolasetron*	**Neurokinin (NK) Receptor Antagonists** *e.g., Fosaprepitant (prodrug → aprepitant)*	**Corticosteroids** (*e.g., dexamethasone, methylprednisolone*)
M.O.A	5-HT_3-receptor blockade (Central & Peripheral)	Highly selective NK_1 receptor antagonist	not well characterized
Indic.	ϴ Emesis (postoperative& chemo).		
		alone or in combination with 5-HT3-receptor antagonists	
S.E.	Headache, dizziness, and *constipation*		Dexamethasone: hiccup

	D_2 Receptor Antagonists *(e.g., droperidol, metochlopramide, prochlorperazine, promethazine, domperidone)*	**Antihistaminics** *(e.g., Meclizine,, diphenhydramine, dimenhydrinate)* **Anticholinergics** *(e.g., Hyoscine)*
M.O.A	▪ D2-receptor blockade (Central) ▪ Antihistaminic & anticholinergic activities (except *metochlopramide)*	Blockade of central H_1 (antihistaminics) and M_1 receptors (anticholinergic)
Indic.	Θ Emesis (chemo-induced) "Droperidol is the most effective"	Θ motion sickness *Hyoscine:* Pre-anesthetic medication. *Antihistaminics*: NV of pregnancy-induced emesis "Cat. B")
S.E.	Acute extrapyramidal SE "dystonia, akathisia & dyskinesia" *Promethazine:* sedation *Droperidol & domperidone*: QT interval prolongation	1) dizziness, sedation, confusion (antihistaminics). 2) anticholinergic side effects & sedation (hyoscine).

Diarrhea

➢Too rapid evacuation of too fluid stools

In diarrhea:

1) Increased osmotic load within the intestine (resulting in retention of water within the lumen).
2) Excessive secretion of electrolytes and water into the intestinal lumen.
3) Exudation of protein and fluid from the mucosa.
4) Altered intestinal motility resulting in rapid transit (thus decreased fluid absorption).

Antidiarrheal Agents

1) Antimotility and Antisecretory Agents:

- Opoids.
- Antimuscarinic Agents.

2) Agents that increase the viscosity of the GI contents.

	Antimotility and Antisecretory Agents Opoids (*e.g.*, Loperamide, Diphenoxylate)	**Agents that increase the viscosity of the GIT contents** *e.g.*, Kaolin (hydrated magnesium aluminum silicate), Pectin (indigestible carbohydrate)
M.O.A	++ of mu opioid receptors →inhibition of myenteric cholinergic transmission→ ↑ colonic transit time and fecal water absorption ***Loperamide is the first choice antidiarrheal (higher selectivity & d*oes *not cross the BBB*) **Higher doses of diphenoxylate) have CNS effects & prolonged use can potentially lead to opioid dependence	adsorbents of bacteria, toxins, and fluid, thereby decreasing stool liquidity

Constipation

- decreased frequency of defecation.
- *or* difficulty in initiation or passage of feces.
- *or* passage of firm feces.
- *or* feeling of incomplete evacuation.

Causes:

1) Lack of dietary fiber.
2) Drug-induced.
3) Disease-induced.

Management:

Constipation is best prevented by:

- High fiber diet, adequate fluid intake
- Regular exercise.
- Heeding of nature's call!!

Drug therapy of constipation

***Drug Classes*:**

1)BULK-FORMING LAXATIVES

2)OSMOTIC LAXATIVES

3)STIMULANT (Irritant) LAXATIVES

4)FECAL SOFTENERS (SURFACTANTS)

	BULK-FORMING LAXATIVES *e.g., Bran, psyllium, methylcellulose (natural plant products), polycarbophil (synthetic fibers)*	**OSMOTIC LAXATIVES**	
		e.g., magnesium sulfate, magnesium hydroxide, magnesium citrate, sodium phosphate	**Sugars** *e.g.,* Lactulose, sorbitol, mannitol
M.O.A	Indigestible, hydrophilic colloids (absorb water), → bulky, emollient gel → distends the colon → promotes peristalsis	• Osmotically mediated water retention → peristalsis • Magnesium → release of cholecystokinin → fluid retention	Non-digestible non-absorbable → hydrolyzed in the colon → low molecular weight acids → osmotically drawing water into the lumen → propulsive motility

	STIMULANT (Irritant) LAXATIVES *e.g.,* *Castor oil, Aloe, Senna, Bisacodyl*	**FECAL SOFTENERS** ➢Surfactants *(e.g., docusate)* ➢Lubricants *(e.g., glycerin, mineral oil)*
M.O.A	Induce a low-grade inflammation → accumulation of water and electrolytes → motility	*Surfactants:* Soften stool material, permitting water to penetrate. *Lubricants:* Lubricates fecal material, retarding water absorption from the stool.
SE	Destruction of the myenteric plexus → colonic atony and dilation→ dependence	• Long-term use of lubricants can impair absorption of fat-soluble vitamins (A, D, E, K).

Laxative Abuse

diarrheal loss of electrolytes and water → ↑aldosterone → ↑ renal excretion of K^+ → hypokalemia → bowel atony → repeated laxative administration